

MANFRED T. REETZ ET AL.
USSN 09/463,494
REPLY TO OFFICE ACTION DATED SEPTEMBER 12, 2005
AMENDMENT OF MARCH 13, 2006

CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefor. The Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

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REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

At the outset, Applicants acknowledge with appreciation the courtesy of the interview recently accorded Applicants' representative. Although agreement was not reached, the interview did clarify certain questions Applicants' representative had.

New claims 48-51 are added. These claims are supported by the instant specification, for example, in the paragraph bridging pages 6-7, discussing the extension of the present invention to the preparation of mutant hydrolase libraries, which, of necessity, would contain a plurality of mutant hydrolases, as claimed in claims 48-51. Applicants do not believe that claims 48-51 introduce new matter.

The sole issue for consideration is the rejection of claims 42-47 under 35 U.S.C. §103(a) as being obvious over either of Nakanishi, et al. (N), Hirose, et al. (U-2) or Krainev, et al. (V-2) in view of Williams, et al. (A), Zhou, et al. (U), Leung, et al. (V), Cadwell, et al. (W), and Shinkai, et al. (X) and further in view of Armstrong et al. (U-3), Kovach, et al. (V-3), Kim, et al.

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(U-3) and Janes, et al. (X-3). In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

1. **The cited references reveal no teaching or suggestion that would have led persons skilled in the art to combine the references in a manner so as to achieve the instantly claimed invention.**

The Examiner cites a number of references allegedly showing various aspects of the claimed invention. However, absent is any suggestion that the references should be combined in such a way as to achieve the present invention. Thus, although the Examiner finds, for example, references teaching mutagenizing PCR and other references teaching spectrophotometry to screen hydrolases, there is no hint or suggestion in any of them that these procedures should be combined, or that such a combination affords the clear advantages that have been described in the instant specification for the present invention.

According to *Manual of Patent Examining Procedure* ("MPEP") § 2143:

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference

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or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.”

Moreover, as reaffirmed by the Court in *In re Regel et al.*, 188 USPQ 136, 139, footnote 5 (CCPA 1975):

“The mere fact that it is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination.”

The cited combination of references contains nothing that suggests the desirability of the proposed combination. As indicated above, the Examiner has cited various groups of references to show various features of the broad method, but neither group of reference contains any hint or suggestion of a procedure allegedly taught by another group of references, and, consequently, there is no teaching or suggestion of the desirability of combining the respective disclosures of the references in any manner that would have yielded the present invention.

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Indeed, the cited references disclose no more than Applicants have clearly taught in the specification was the state of the art. Thus, Applicants do not claim to have invented either mutagenizing PCR or spectrophotometry. What Applicants have done, and what is their contribution to the art, is to combine these techniques in a way that solves a long-standing problem of how to adapt *in vitro* evolution to practical use. (See, for example, the last paragraph on page 3 of the instant specification, describing the failure of *in vitro* evolution to date in the context of screening combinatorial mutant lipase libraries for improved stereoselectivity.

For obviousness, there must be some teaching or suggestion in the prior art references motivating persons skilled in the art to combine them to achieve the present invention. The mere fact that the techniques were separately known in the art does not suggest their combination. Moreover, where, as here, Applicants have shown clear advantages resulting from such combination, namely the successful adaptation of *in vitro* evolution to the production and identification of hydrolases having improved properties, obviousness additionally requires some teaching or suggestion in the combination of such improved results.

Respectfully, the cited references do not, in and of themselves, suggest their combination into an integrated process having the features instantly claimed. Certainly, there is no hint in the combination of references of the advantages clearly obtained upon the successful completion of the present invention.

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In view of the foregoing, Applicants submit that the Examiner would be fully justified to reconsider and withdraw this rejection on this basis alone.

2. All claim limitations have not been dealt with.

During the course of the interview, it became clear that it was the Examiner's opinion that Applicants had not focused the Examiner's attention on distinguishing limitations of, especially, the dependent claims. In response, Applicants would remind the Examiner that, as should be clear from the quote above, all claim limitations must be dealt with. This clearly includes not only the limitations of the independent claims, but also the limitations of any rejected dependent claim as well.

Claim 45 in step c) requires producing a recombinant hydrolase gene by enzymatically *fragmenting* a plurality of mutant hydrolase genes or a mixture of at least one starting hydrolase gene and at least one mutant hydrolase gene *to produce a plurality of gene fragments*, and then *recombining the gene fragments* to yield the recombinant hydrolase gene. So far as Applicants can tell, the Examiner has not dealt with this limitation at all. Thus, the Examiner has not shown where in any of the cited references, a mutant hydrolase gene has been produced in this manner, and then subjected to screening for improved properties. Absent such teaching in the cited

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references, claims 45-47 could not possibly have been *prima facie* obvious over the cited combination of references.

The Examiner also has never dealt with the requirements of claims 44 and 47 that the starting hydrolase gene is a hydrolase gene *that has been previously mutagenized in a PCR* previously performed in accordance with step b). Clearly, these claims cover the application of multiple rounds of mutagenizing PCR in the improvement of hydrolase properties. Again, the Examiner has not dealt with this limitation and shown it at least to have been described in the cited prior art. In the absence of any teaching or suggestion of this feature, Applicants submit that claims 44 and 47 also could not have been *prima facie* obvious in view of the cited combination of references.

3. Special consideration should be given to new claims 48-51.

With the exception of Janes, the four tertiary references appear to use spectrophotometry to screen a single enzyme. Janes mentions screening multiple enzymes, but these are stated to be in Jane's very first paragraph "commercial enzymes." Thus, even in Janes, there is no teaching or suggestion of the use of spectrophotometry to screen a plurality of mutant hydrolases as part of a directed evolution process. Claims 48-51 clearly require the use of spectrophotometry in

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this context, and, consequently, are not *prima facie* obvious over the cited combination of references, even including Janes.

In view of the foregoing, Applicants submit that the Examiner would be fully justified to reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

If this rejection is maintained, Applicants respectfully request that the Examiner make findings as to all limitations of all rejected claims as discussed above.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

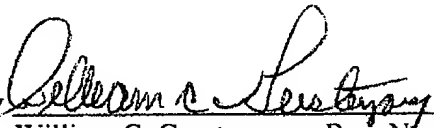
Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

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Early and favorable action is earnestly solicited.

Respectfully submitted,

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